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(54) Preparation for promoting hair growth.

(57) A preparation for promoting hair growth is disclosed, which contains as an effective ingredient or ingredients one or more compounds selected from the group consisting of purine compounds, pyridylurea compounds, diphenylurea compounds, pyrimidine compounds, imidazole compounds, benzoylaminourea compounds and 4-substituted aminopyrrolo[2,3-d]pyrimidine compounds. This preparation exhibits an excellent effect of promoting hair growth or curing alopecia such as male alopecia or alopecia areata. Of the effective compounds, purine compounds and pyridyl compounds exhibit particularly remarkable effects.

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This invention relates to a preparation for promoting hair growth containing, as an effective ingredient, a material showing remarkable effects of promoting hair growth and curing alopecia such as male alopecia or alopecia areata.

Many preparations for promoting hair growth have conventionally been used for prophylaxis or treatment of baldness and thinning of hair.

Ingredients contained in a preparation for promoting hair growth are generally intended to improve the circulation of the blood in scalp, attain cleaning, anti-inflammation and sterilization of scalp, activate enzymes of cells constituting hair follicles and surrounding tissue, improve energy metabolism of hair-matrix cells and depress the action of male sex hormone in scalp. For example, carpronium chloride, vitamin E, an extract of Capsieum annuum L., an extract of Japanese chirata and a garlic extract have been intended to increase the amount of blood stream in hair follicles based on their vasodilative action on peripheral blood vessel, thereby to activate hair-matrix cells. Since alopecia is known to be induced by inflammation, anti-inflammatory agents such as glycyrrhizin and allantoin and germicides such as hinokitiol and resorcin have been used for preventing inflammation or production of decomposition products which might be produced by bacteria from scurf or sebum and which can induce inflammation. Vitamins such as vitamin A, vitamin B group, biotin and pantothenic acid derivatives have been used for activating enzymes of hair-matrix cells to promote synthesis of hair, pentadecanoic acid glyceride has been used for improving energy metabolism of hair-matrix cells, and female sex hormones such as estradiol and ethynylestradiol have been used for depressing the action of male sex hormone which is believed to be the primary cause of male alopecia.

However, all of these conventional ingredients contained in a preparation for promoting hair growth have failed to give a satisfactory result, though they exhibit a hair growth-promoting effect or an alopecia-preventing effect to some extent. In particular, they fail to exhibit an enough effect of promoting hair growth and curing alopecia.

With the above-described situation in mind, the inventors have made intensive investigations and, as a result, have found ingredients exhibiting a remarkable effect of promoting hair growth, thus having completed the invention.

Summary of the Invention

It is an object of the present invention to provide a preparation for promoting hair growth which, when applied to scalp, exhibits a marked effect of promoting hair growth and curing male alopecia or alopecia areata.

Other objects, features and advantages of the present invention will become apparent from the detailed description of the preferred embodiments of the invention to follow.

Detailed Description of the Preferred Embodiments of the Invention

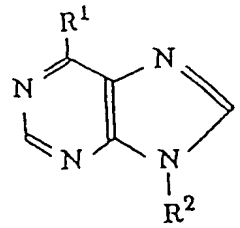
The mechanism of how alopecia is induced has not yet been clarified in detail. However, main factors which are at present considered to induce alopecia are as follows:

1. Acatastasia of physiological functions of scalp;
2. Depression of metabolism function in hair follicles and hair bulb;
3. Depression of the function of hair follicles due to male sex hormone action in sebaceous gland, hair follicles and hair root;
4. Mental stress; and
5. Others such as genetic factors and disease factors.

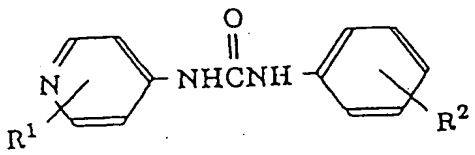
In addition, aging is believed to accelerate epilation and it is also believed that, as hair-matrix cells age, they suffer depression of cell division ability and cell differentiation ability and depression of every metabolic activity including blood stream amount in localized areas, leading to thinning of hair and epilation.

The preparation of the present invention for promoting hair growth is particularly effective for male alopecia and alopecia areata which are seemingly induced by depression of the function of hair follicles.

The effective ingredients contained in the preparation of the present invention are represented by the following general formulae (1) to (7):



(1)



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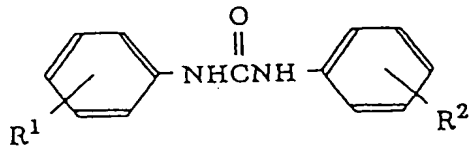

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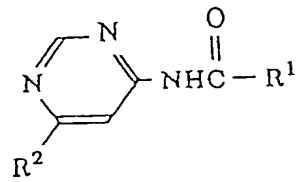

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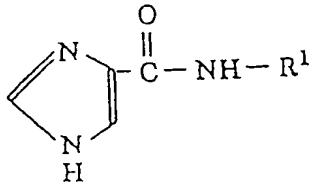

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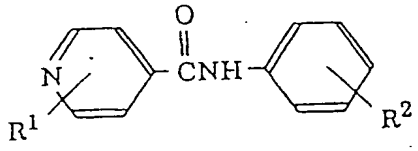

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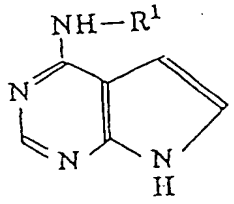


(7)

In the above general formula (1), examples of the substituent represented by R^1 include an alkyl group (containing 1 to 22, preferably 1 to 12, carbon atoms and being straight or branched; e.g., a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a pentyl group, a hexyl group, a heptyl group, an octyl group, a nonyl group or a dodecyl group), a cyclic hydrocarbon group (e.g., a 2-cyclohexylethyl group, a cyclohexyl group, a cyclohexylmethyl group, a cyclopentyl group, a cyclopentylmethyl group or a 2-cyclopentylethyl group), an alkenyl group (containing 1 to 22, preferably 1 to 12, carbon atoms and being straight or branched; e.g., a vinyl group, an allyl group, a 2-butenyl group or an isoprenyl group), a substituted or non-substituted aralkyl group [a benzyl group (e.g., a benzyl group, a 2-methylbenzyl group, a 4-methylbenzyl group, a 4-ethylbenzyl group, a 3-chlorobenzyl group, a 4-fluorobenzyl group or a 4-nitrobenzyl group), a phenylethyl group (e.g., a phenylethyl group, a 2-methylphenylethyl group, a 4-methylphenylethyl group, a 4-ethylphenylethyl group, a 3-chlorophenylethyl group, a 4-fluorophenylethyl group, a 4-nitrophenylethyl group, a 4-propylphenylethyl group, a 3,5-difluorophenylethyl group, a 4-nitrophenylethyl group, a 2-cyanophenylethyl group, a 4-dimethylaminophenylethyl group, a 4-methoxyphenylethyl group, a 3-trimethylsilyloxyphenylethyl group, a 4-trifluoromethylphenylethyl group, a 4-butyldimethylsilyloxyphenylethyl group, a 2-methylthiophenylethyl group or a 4-trimethylsilyloxyphenylethyl group), a substituted or non-substituted styryl group (e.g., a styryl group, a 2-methylstyryl group, a 4-methylstyryl group, a 4-ethylstyryl group, a 3-chlorostyryl group, a 4-fluorostyryl group, a 4-nitrostyryl group, a 4-propylstyryl group, a 3,5-

difluorostyryl group, a 4-nitrostyryl group, a 2-cyanostyryl group, a 4-dimethylaminostyryl group, a 4-methoxystyryl group, a 3-trimethyloxystyryl group, a 4-trifluoromethylstyryl group, a 4-butyldimethylsilyloxystyryl group, a 2-methylthiostyryl group or a 4-trimethylsilyloxystyryl group), an alkylamino group (represented by -NRR' wherein R and R' may be the same or different and each represents an alkyl group containing 1 to 22, preferably 1 to 12, carbon atoms and being straight or branched, such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a pentyl group, an isopentyl group, a 3-methylpentyl group, a hexyl group, a 2-ethylhexyl group, a heptyl group, an octyl group, a nonyl group or a dodecyl group), an amino group having a cyclic hydrocarbon group (represented by -NH-R wherein R represents, for example, a 2-cyclohexylethyl group, a cyclohexyl group, a 3-cyclohexylpropyl group, a 2-cyclohexylpropyl group, a cyclohexylmethyl group, a cyclopentyl group, a cyclopentylmethyl group or a 2-cyclopentylethyl group), an alkenylamino group (represented by -NH-R wherein R represents an alkenyl group containing 1 to 22, preferably 1 to 12, carbon atoms and being straight or branched, such as a vinyl group, an allyl group, a 2-butenyl group, an isoprenyl group, a 3-methyl-2-butenyl group or a 3-ethyl-2-pentenyl group), a substituted or non-substituted benzylamino group (represented by -NH-R wherein R represents, for example, a benzyl group, a 2-methylbenzyl group, a 3-methylbenzyl group, a 4-methylbenzyl group, a 4-ethylbenzyl group, a 3-chlorobenzyl group, a 4-chlorobenzyl group, a 2,4-dichlorobenzyl group, a 2-hydroxybenzyl group, a 3-fluorobenzyl group, a 4-nitrobenzyl group, a 4-bromobenzyl group, a 4-fluorobenzyl group, a 3-nitrobenzyl group, a 4-propylbenzyl group, a 3,5-difluorobenzyl group, a 2-cyanobenzyl group, a 2-acetaminobenzyl group, a 4-acetaminobenzyl group, a 4-methoxycarbonylbenzyl group, a 4-dimethylaminobenzyl group, a 4-methoxybenzyl group, a 3-trimethylsilyloxybenzyl group, a 3-trifluoromethylbenzyl group, a 4-butyldimethylsilyloxybenzyl group, a 2-methylthiobenzyl group, a 4-trimethylsilyloxybenzyl group or a 4-methylthiobenzyl group), a substituted or non-substituted phenylethylamino group (represented by -NH-R wherein R represents, for example, a phenylethyl group, a 2-methylphenylethyl group, a 4-methylphenylethyl group, a 4-ethylphenylethyl group, a 3-chlorophenylethyl group, a 4-fluorophenylethyl group, a 4-nitrophenylethyl group, a 4-propylphenylethyl group, a 3,5-difluorophenylethyl group, a 3-nitrophenylethyl group, a 2-cyanophenylethyl group, a 4-dimethylaminophenylethyl group, a 4-methoxyphenylethyl group, a 3-trimethylsilyloxyphenylethyl group, a 4-trifluoromethylphenylethyl group, a 4-butyldimethylsilyloxyphenylethyl group, a 2-methylthiophenylethyl group or a 4-trimethylsilyloxyphenylethyl group), a substituted or non-substituted phenylamino group (represented by -NH-R wherein R represents, for example, a phenyl group, a 2-methylphenyl group, a 3-methylphenyl group, a 4-methylphenyl group, 4-ethylphenyl group, a 3-chlorophenyl group, a 4-chlorophenyl group, a 2,4-dichlorophenyl group, a 2-hydroxyphenyl group, a 3-fluorophenyl group, 4-nitrophenyl group, a 4-bromophenyl group, a 4-fluorophenyl group, a 3-nitrophenyl group, a 4-propylphenyl group, a 3,5-difluorophenyl group, a 2-cyanophenyl group, a 2-acetaminophenyl group, a 4-acetaminophenyl group, a 4-methoxycarbonylphenyl group, a 4-dimethylaminophenyl group, a 4-methoxyphenyl group, a 3-trimethylsilyloxyphenyl group, a 4-trifluoromethylphenyl group, a 4-butyldimethylsilyloxyphenyl group, a 2-methylthiophenyl group, a 4-trimethylsilyloxyphenyl group or a 4-methylthiophenyl group), a substituted or non-substituted phenylaminocarbonylamino group (represented by -NH-R wherein R represents, for example, a phenylaminocarbonyl group, a 2-methylphenylaminocarbonyl group, a 3-methylphenylaminocarbonyl group, a 4-methylphenylaminocarbonyl group, a 4-ethylphenylaminocarbonyl group, a 3-chlorophenylaminocarbonyl group, a 4-chlorophenylaminocarbonyl group, a 2,4-dichlorophenylaminocarbonyl group, a 2-hydroxyphenylaminocarbonyl group, a 3-fluorophenylaminocarbonyl group, a 4-nitrophenylaminocarbonyl group, a 4-bromophenylaminocarbonyl group, a 4-fluorophenylaminocarbonyl group, a 2-cyanophenylaminocarbonyl group, a 2-acetaminophenylaminocarbonyl group, a 4-methoxycarbonylphenylaminocarbonyl group, a 4-dimethylaminophenylaminocarbonyl group, a 4-methoxyphenylaminocarbonyl group, a 3-trimethylsilyloxyphenylaminocarbonyl group, a 4-trifluoromethylphenylaminocarbonyl group, a 4-butylmethylsilyloxyphenylaminocarbonyl group, a 2-methylthiophenylaminocarbonyl group, a 4-trimethylsilyloxyphenylaminocarbonyl group or a 4-methylthiophenylaminocarbonyl group), a 4-hydroxy-3-methyl-2-butenyl group, a 4-acetoxy-3-methyl-2-butenyl group, a 4-propionyloxy-3-methyl-2-butenyl group, a 4-butyryloxy-3-methyl-2-butenyl group, a 2-chloro-5-methyl-1-pentenyl group, a 2-pyridyl group, a 2-pyridylmethyl group, a 3-pyridylmethyl group, a 4-pyridylmethyl group, a 2-pyrrolylmethyl group, a 4-oxazolylmethyl group, a 2-imidazolylmethyl group, a 3-pyridazyl group, a 3-pyridazylmethyl group, a 1-naphthyl group, a 1-naphthylmethyl group, a 2-naphthyl group and a 2-naphthylmethyl group, and examples of the substituent represented by R^2 include a hydrogen atom, a pentose residue (e.g., a 1-ribofuranosyl group, a 1-lyxofuranosyl group, a 1-xylofuranosyl group or a 1-arabofuranosyl group) and a hexose residue (e.g., a

1 – glucosyl group, a 1 – galactosyl group, a 1 – gulosyl group, a 1 – mannosyl group or a 1 – allosyl group).

In the above general formula (2), examples of the substituents R^1 and R^2, which may be the same or different, include a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, a chlorine atom, a hydroxy group, a fluorine atom, a nitro group, a bromine atom, a cyano group, an acetamino group, a methoxycarbonyl group, a dimethylamino group, a methoxy group, a trifluoromethyl group, a butyldimethylsilyloxy group, a methylthio group, a trimethylsilyloxy group, an acetoxy group, a propionyloxy group, a methylsulfinyl group, a methylsulfonyl group, a carboxyl group, a methoxycarbonyl group and an ethoxycarbonyl group.

In the above general formula (3), examples of the substituents R^1 and R^2, which may be the same or different, include a hydrogen atom, a methyl group, an ethyl group, a butyl group, a propyl group, a chlorine atom, a hydroxy group, a fluorine atom, a nitro group, a bromine atom, a cyano group, an acetamino group, a methoxycarbonyl group, a dimethylamino group, a methoxy group, a trimethylsilyloxy group, a trifluoromethyl group, a butyldimethylsilyloxy group, a methylthio group, an acetoxy group, a propionyloxy group, a methylsulfinyl group, a methylsulfonyl group, a carboxyl group, a methoxycarbonyl group and an ethoxycarbonyl group.

In the above general formula (4), examples of the substituent represented by R^1 include a substituted or non – substituted phenyl group (e.g., a phenyl group, a 2 – methylphenyl group, a 3 – methylphenyl group, a 4 – methylphenyl group, a 4 – ethylphenyl group, a 3 – chlorophenyl group, a 4 – chlorophenyl group, a 2,4 – dichlorophenyl group, a 2 – hydroxyphenyl group, a 3 – fluorophenyl group, a 4 – nitrophenyl group, a 4 – bromophenyl group, a 4 – fluorophenyl group, a 3 – nitrophenyl group, a 4 – propylphenyl group, a 3,5 – difluorophenyl group, a 2 – cyanophenyl group, a 2 – acetaminophenyl group, a 4 – acetaminophenyl group, a 4 – methoxycarbonylphenyl group, a 4 – dimethylaminophenyl group, a 4 – methoxyphenyl group, a 3 – trimethyloxyphenyl group, a 4 – trifluoromethylphenyl group, a 4 – butyldimethylsilyloxyphenyl group, a 2 – methylthiophenyl group, a 4 – trimethylsilyloxyphenyl group or a 4 – methylthiophenyl group) and a substituted or non – substituted anilino group (e.g., an anilino group, a 2 – methylanilino group, a 3 – methylanilino group, a 4 – methylanilino group, a 4 – ethylanilino group, a 3 – chloroanilino group, a 4 – chloroanilino group, a 2,4 – dichloroanilino group, a 2 – hydroxyanilino group, a 3 – fluoroanilino group, a 4 – nitroanilino group, a 4 – bromoanilino group, a 4 – fluoroanilino group, a 3 – nitroanilino group, a 4 – propylanilino group, a 3,5 – difluoroanilino group, a 2 – cyanoanilino group, a 2 – acetaminoanilino group, a 4 – acetaminoanilino group, a 4 – methoxycarbonylanilino group, a 4 – dimethylaminoanilino group, a 4 – methoxyanilino group, a 3 – trimethylsilyloxyanilino group, a 4 – trifluoromethylanilino group, a 4 – butyldimethylsilyloxyanilino group, a 2 – methylthioanilino group, a 4 – trimethylsilyloxyanilino group or a 4 – methylthioanilino group) and examples of the substituent represented by R^2 include a hydrogen atom, a methyl group, an ethyl group, a butyl group, a propyl group, a chlorine atom, a hydroxy group, a fluorine atom, a nitro group, a bromine atom, a cyano group, an acetamino group, a methoxycarbonyl group, a dimethylamino group, a methoxy group, a trimethyloxy group, a trifluoromethyl group, a butyldimethylsilyloxy group, a methylthio group, a trimethylsilyloxy group, an acetoxy group, a propionyloxy group, a methylsulfinyl group, a methylsulfonyl group, a carboxyl group, a methoxycarbonyl group and an ethoxycarbonyl group.

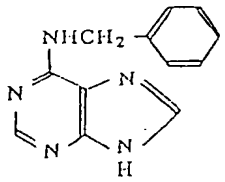
In the above general formula (5), examples of the substituent represented by R^1 include a substituted or non – substituted phenyl group (e.g., a phenyl group, a 2 – methylphenyl group, a 3 – methylphenyl group, a 4 – methylphenyl group, a 4 – ethylphenyl group, a 3 – chlorophenyl group, a 4 – chlorophenyl group, a 2,4 – dichlorophenyl group, a 2 – hydroxyphenyl group, a 3 – fluorophenyl group, a 4 – nitrophenyl group, a 4 – bromophenyl group, a 4 – fluorophenyl group, a 3 – nitrophenyl group, a 4 – propylphenyl group, a 3,5 – difluorophenyl group, a 2 – cyanophenyl group, a 2 – acetaminophenyl group, a 4 – acetaminophenyl group, a 4 – methoxycarbonylphenyl group, a 4 – dimethylaminophenyl group, a 4 – methoxyphenyl group, a 3 – trimethylsilyloxyphenyl group, a 4 – trifluoromethylphenyl group, a 4 – butyldimethylsilyloxyphenyl group, a 2 – methylthiophenyl group, a 4 – trimethylsilyloxyphenyl group or a 4 – methylthiophenyl group).

In the above general formula (6), examples of the substituent represented by R^1 include a hydrogen atom, a 2 – methyl group, a 3 – methyl group, a 2 – ethyl group, a 2 – chloro atom, a 3 – chloro atom, 2,6 – dichloro atoms, a 2 – hydroxy group, a 2 – fluoro atom, a 2 – nitro group, a 2 – bromo atom, a 2 – fluoro atom, a 3 – nitro group, a 2 – propyl group, 2,6 – difluoro atoms, a 2 – cyano group, a 2 – acetamino group, a 3 – acetamino group, a 2 – methoxycarbonyl group, a 2 – dimethylamino group, a 2 – methoxycarbonyl group, a 2 – dimethylamino group, a 2 – methoxy group, a 2 – trimethylsilyloxy group, a 2 – trifluoromethyl group, a 2 – butyldimethylsilyloxy group, a 2 – methylthio group, a 2 – trimethylsilyloxy group, a 2 – methylthio group, a 2 – acetoxy group, a 2 – propionyloxy group, a 2 – methylsulfinyl group, a 2 – methylsulfonyl group, a 2 – carboxyl group, a 2 – methoxycarbonyl group and a 2 – ethoxycarbonyl group, and examples of the substituent represented by R^2 include a hydrogen atom, a methyl group, an ethyl group, a butyl group, a

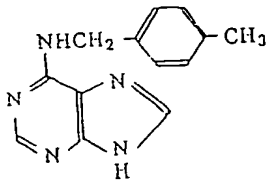
propyl group, a chlorine atom, a hydroxy group, a fluorine atom, a nitro group, a bromine atom, a cyano group, an acetamino group, a methoxycarbonyl group, a dimethylamino group, a methoxy group, a trifluoromethyl group, a butyldimethylsilyloxy group, a methylthio group, a trimethylsilyloxy group,an acetoxy group, a propionyloxy group, a methylsulfinyl group, a methylsulfonyl group, a carboxyl group, a methoxycarbonyl group and an ethoxycarbonyl group.

In the above general formula (7), examples of the substituent represented by R^1 include a benzyl group (e.g., a benzyl group, a 2 – methylbenzyl group, a 3 – methylbenzyl group, a 4 – methylbenzyl group, a 4 – ethylbenzyl group, a 3 – chlorobenzyl group, a 4 – chlorobenzyl group, a 2,4 – dichlorobenzyyl group, a 2 – hydroxybenzyl group, a 3 – fluorobenzyl group, a 4 – nitrobenzyl group, a 4 – bromobenzyl group, a 4 – fluorobenzyl group, a 3 – nitrobenzyl group, a 4 – propylbenzyl group, a 3,5 – difuorobenzyl group, a 2 – cyanobenzyl group, a 2 – acetaminobenzyl group, a 4 – acetaminobenzyl group, a 4 – methoxycarbonylben – zyl group, a 4 – dimethylaminobenzyl group, a 4 – methoxybenzyl group, a 3 – trimethylsilyloxybenzyl group, a 4 – trifluoromethylbenzyl group, a 4 – butyldimethylsilyloxybenzyl group, a 2 – methylthiobenzyl group, a 4 – trimethylsilyloxybenzyl group, a 4 – methylthiobenzyl group) and a substituted or non – substituted phenylaminocarbonyl group.

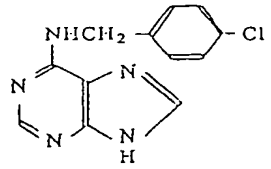
The compounds of the present invention are specifically illustrated below.



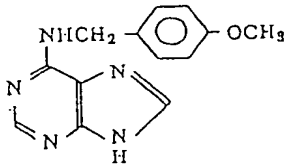
6-benzylaminopurine



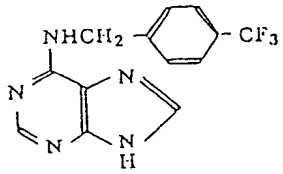
6-(4-methylbenzylamino)purine



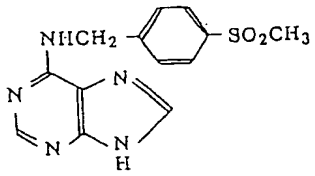
6-(4-chlorobenzylamino)purine



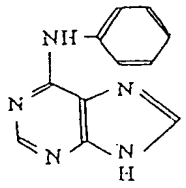
6-(4-methoxybenzylamino)-purine



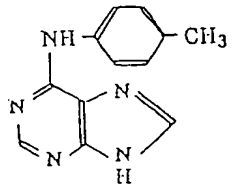
6-(4-trifluoromethylbenzyl-amino)purine



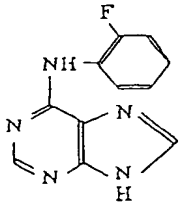
6-(4-methylsulfonylbenzyl-amino)purine



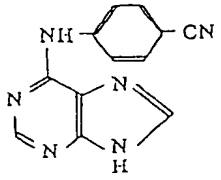
6-phenylaminopurine



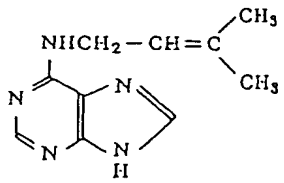
6-(4-methylphenylamino)purine



6-(2-fluorophenylamino)-purine



6-(4-cyanophenylamino)purine



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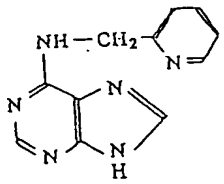

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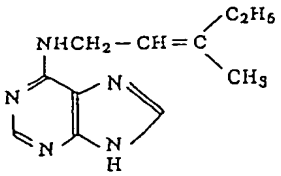

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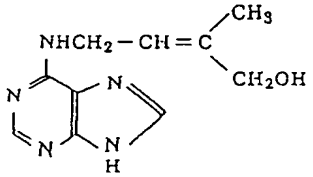

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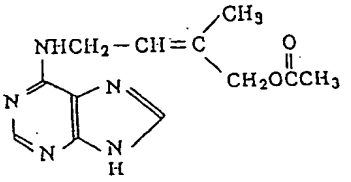

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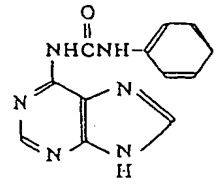
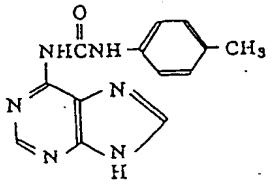


6-(phenylureido)purine



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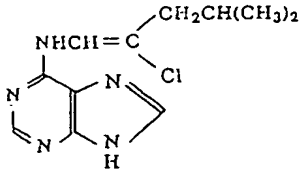

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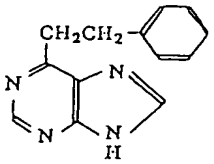
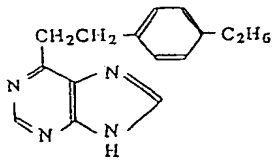
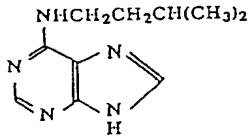


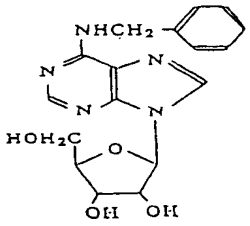
6-(2-phenethyl)purine



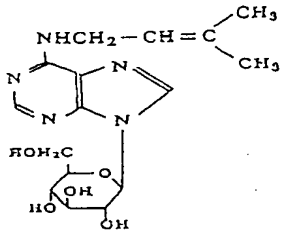
6-(4-ethyl-2-phenethyl)-purine



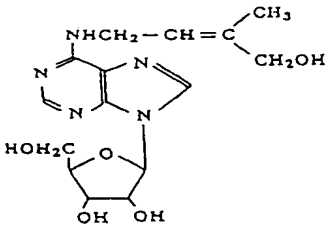
6-isoamylaminopurine



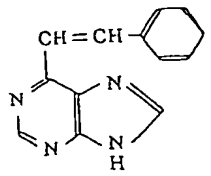
6-benzylamino-9-ribofuranosylpurine



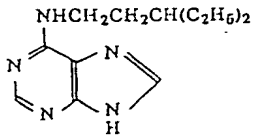
6-(3-methyl-2-butenylamino)-9-glucosylpurine



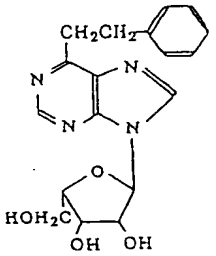
6-(4-hydroxy-3-methyl-2-butenyl amino)-9-ribofuranosylpurine



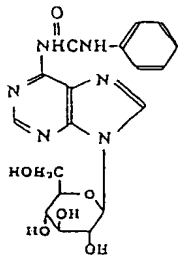
6-styrylpurine



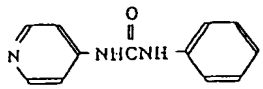
6-(3-ethylpentylamino)purine



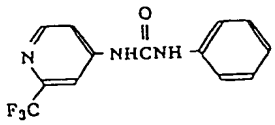
6-(2-phenethyl)-9-lyxofranosylpurine



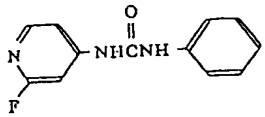
6-phenylureido-9-glucosylpurine



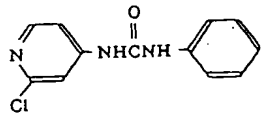
N-(4-pyridyl)-N'-phenylurea



N-(2-trifluoromethyl-4-pyridyl)-N'-phenylurea



N-(2-fluoro-4-pyridyl)-N'-phenylurea



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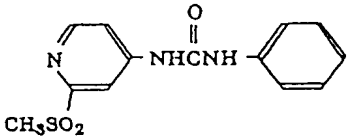
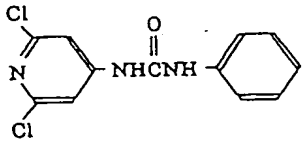
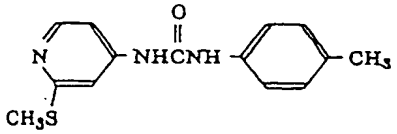


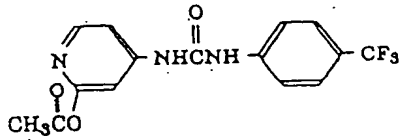
N-(2-methylsulfonyl-4-pyridyl)-N'-phenylurea



N-(2,6-dichloro-4-pyridyl)-N'-phenylurea



N-(2-methylthio-4-pyridyl)-N'-(4-methylphenyl)urea



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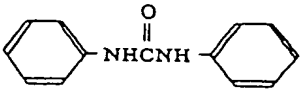
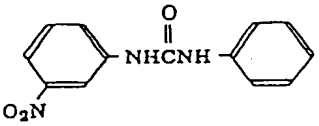
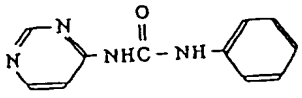


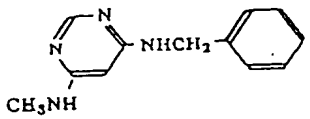
diphenylurea



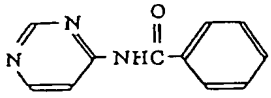
N-(3-nitrophenyl)-N'-phenylurea



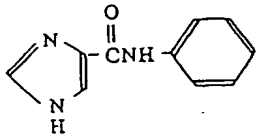
phenylureido-4-pyrimidine



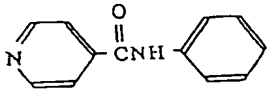
4-benzylamino-6-methylamino-pyrimidine



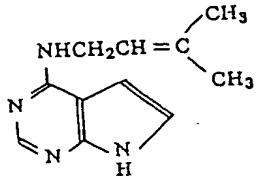
4-benzoylaminopyrimidine



4-imidazolecarbanilide



isonicotinic acid anilide



4-(3-methyl-2-butenylamino)-pyrrolo[2,3-d]pyrimidine

The above-described compounds to be used in the present invention may be obtained as chemically synthesized compounds or as natural products. Extracts containing these compounds may also be used. As the natural products, there are illustrated various parts of various plants, particularly coconuts milk, corn seeds, immature fruits of horse-chestnut (Aesculus hippocastanum L.), bananas and apples, roots of chicory (Chichorium intybus L.), seeds of lupine, and leaves of poplar. Illustrative of the extracts are a hydrolyzate of yeast DNA, an extract of herring spermatozoa and an extract of a culture liquor of fungi, an extract of various transfer RNA and an extract of Corynebacterium fascians.

Of the above-described compounds to be used as effective ingredients in the present invention, those represented by the general formula (1) exhibit particularly remarkable effects. The compounds to be used as effective ingredients may be used independently or may be used in combination of two or more for attaining an enhanced effect of promoting hair growth or curing alopecia such as male alopecia or alopecia areata.

The preparation of the present invention for external use includes a medicine, a quasi-drug and a cosmetic and may be in various known forms which permit external application, such as cream, lotion, emulsion, ointment, gel, hair tonic, hair liquid, liniment, hair rinse, hair shampoo, hair treatment, hair conditioner, aerosol and mousse. As a base for the preparation, any liquid or solid material acceptable for application to hair may be used. If necessary, there may be added to the preparation various additives such as an antiseptic, a perfume, a stabilizing agent, a colorant, an ultraviolet ray absorbent, an antioxidant, a humectant, a thickening agent, etc.

Illustrative of the antiseptic are benzoic acid salts, salicylic acid salts, sorbic acid salts, dehydroacetic acid salts, p-hydroxybenzoic acid esters, 2,4,4'-trichloro-2'-hydroxydiphenyl ether, 3,4,4'-trichlorocarbanide, benzalkonium chloride, hinokitiol, resorcin, ethanol, etc.

Illustrative of the stabilizing agent are chelating agents such as ethylenediaminetetraacetic acid salts, pyrrophosphoric acid salts, hexametaphosphoric acid salts, citric acid salts, tartaric acid and gluconic acid and pH-adjusting agents such as sodium hydroxide and potassium hydrogenphosphate.

Illustrative of the ultraviolet ray absorbent are 4-methoxybenzophenone, octyl dimethyl-p-aminobenzoate, ethylhexyl p-methoxycinnamoate, titanium oxide, kaolin and talc.

Illustrative of the anti-oxidant are dibutylhydroxytoluene, butylhydroxyanisole and propyl gallate.

Illustrative of the humectant are polyhydric alcohols (e.g., glycerin, propylene glycol, 1,3-butylene glycol, sorbitol, mannitol, polyethylene glycol and dipropylene glycol), NMF components (e.g., amino acids, sodium lactate and sodium pyrolidonecarboxylate) and water-soluble high-molecular substances (e.g., hyaluronic acid, collagen, elastin, chondroitin sulfate, dermatan sulfate, fibronectin, ceramides, heparin-like

materials and chitosan.

Illustrative of the thickening agent are natural high-molecular materials (e.g., sodium alginate, xanthan gum, aluminum silicate, an extract of semen cydnoniae, tragacanth gum and starch), semi-synthetic high-molecular materials (e.g., methyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, soluble starch and cationized cellulose) and synthetic high-molecular substances (e.g., carboxyvinyl polymer and poly-vinyl alcohol).

As to the amount of the effective ingredient to be contained in the preparation of the present invention may properly be changed depending upon the degree of alopecia and kind of preparation form but, as a general guide, it is contained in an amount of from about 0.0001 to about 20 % by weight, preferably from about 0.01 to about 10 % by weight, based on the preparation.

The effective ingredients may be used alone or may be used in combination of other known chemicals commonly used as effective ingredients for a preparation for promoting hair growth, such as c-AMP and its derivatives, forskolin, carpronium chloride, pentadecanoic acid glyceride, minoxidil and female sex hormones represented by estradiol, for more enhancing the effect of the present invention of promoting hair growth or curing alopecia such as male alopecia or alopecia areata. In addition, cepharanthine, vitamin A, vitamin E, vitmin E nicotinate, vitamin B group compounds (e.g., nicotinic acid, nicotinic acid amide and benzyl nicotinate), other vitamins (e.g., biotin and pantothenic acid derivatives), vasodilators for peripheral blood vessel (e.g., ginger tincture and capsicum tincture), refrigerants (e.g., camphor and menthol), germicides (e.g., hinokitiol, benzalkonium chloride and undecylenic acid), anti-inflammatory agents (e.g., lysozyme chloride, glycyrrhizin and allantoin), cell-activating agents (e.g., an extract of Japanese chirata, an extract of garlic, an extract of ginseng, an extract of scutellaria, an extract of rosemary, an extract of aloe and an extract of placenta), a photosensitizer, protein kinase C inhibitors (e.g., H-7), an extract of P. japonicus C.A.Mey, and extract of cashew and an extract of malt root may properly be selected to use in combination with the effective ingredients of the present invention.

Formulation examples of the preparations of the present invention for promoting hair growth and test examples demonstrating the advantages of the present invention are described below which, however, are not to be construed as limiting the present invention in any way.

Additionally, the term "proper amount" used in the formulation examples means the amount to make the total 100 % by weight.

〈Formulation Example 1〉 Hair cream

		% by weight
A	Liquid paraffin	10.0
	Squalane	7.0
	jojoba oil	3.0
	Solid paraffin	3.0
	Polyoxyethylene cetyl ether	2.0
	Sorbitan sesquioleate	1.0
	Potassium hydroxide	0.1
	6-Styrylpurine	5.0
B	Glycerin	3.0
	Ethylparaben	0.1
	Purified water	proper amount

Ingredients belonging to group A were heated to make solution A. Separately, ingredients belonging to group B were heated to make solution B. The solution B was added to the solution A, and the mixture was stirred to emulsify. The resulting emulsion was cooled to prepare a hair cream.

〈Formulation Example 2〉 Hair tonic

		% by weight
A	Polyoxyethylene hydrogenated castor oil	1.0
	Ginger tincture	1.0
	Isopropylmethylphenol	0.05
	Ethanol	55.0
	6 – Benzylaminopurine	0.5
B	Glycerin	2.0
	Purified water	proper amount

Ingredients belonging to group A were uniformly heated to make solution A. Separately, ingredients belonging to group B were uniformly dissolved and gradually added to solution A, followed by uniform stirring to prepare a hair tonic.

〈Formulation Example 3〉 Hair treatment

		% by weight
A	Avocado oil	5.0
	Squalane	5.0
	Liquid paraffin	10.0
	Stearic acid	3.0
	Glycerin monostearate	3.0
	Hydrous lanolin alcohol	5.0
	6 – Benzylamino – 9 – ribofuranosylpurine	2.0
B	Extract of Japanese chirata	1.0
	1,3 – Butylene glycol	5.0
	Triethanolamine	1.0
	Methylparaben	0.2
	Purified water	proper amount

Ingredients belonging to group A were heated to make solution A. Separately, ingredients belonging to group B were heated to make solution B. The solution B was added to the solution A, and the mixture was stirred to emulsify. The resulting emulsion was cooled to prepare a hair treatment.

〈Formulation Example 4〉 Hair shampoo

		% by weight
A	Vitamin B_{12}	0.05
	N – coconut oil fatty acid – L glutamic acid in triethanolamine (30 %)	40.0
	Coconut oil fatty acid diethanolamide	3.0
	Polyoxyethylene dioleic acid methyl glucoside (120 E.O.)	2.0
	N – (2 – Chloro – 4 – pyridyl) – N' – phenylurea	2.5
B	Ethyl p – hydroxybenzoate	0.3
	Disodium edetate	0.1
	Purified water	proper amount

Ingredients belonging to group A were uniformly stirred to make solution A. Separately, ingredients belonging to group B were uniformly heated and dissolved and gradually added to solution A, followed by

uniform stirring to prepare a hair shampoo.

〈Formulation Example 5〉 Aerosol

		% by weight
A	Benzyl nicotinate	0.01
	Vitamin E acetate	0.05
	Cetanol	1.2
	N – (2 – Trifluoromethyl – 4 – pyridyl) – N' – phenylurea	0.05
	6 – (2 – Phenethyl)purine	0.05
	Propylene glycol	4.0
	Ethanol	8.0
	Purified water	proper amount
B	Liquefied petroleum gas (propellant)	7.0

Ingredients belonging to group A were uniformly mixed to make solution A. The solution A was placed in an aerosol vessel, and the vessel was filled with B in a conventional manner to prepare an aerosol.

〈Formulation Example 6〉 Air foam

		% by weight
A	Hinokitiol	0.1
	Cetanol	1.2
	Propylene glycol	2.0
	Dimethylsilicone oil	2.0
	Polyoxyethylene hardened castor oil	2.5
	Liquid paraffin	1.0
	Polyvinylpyrrolidone	0.5
	N – (2,6 – Dichloro – 4 – pyridyl) – N' – phenylurea	3.0
	Methylparaben	0.2
	Ethanol	10.0
	Purified water	proper amount
B	Liquefied petroleum gas (propellant)	4.0

Ingredients belonging to group A were uniformly mixed and placed in a vessel. The vessel was filled with component B in a conventional manner to prepare an air foam.

〈Formulation Example 7〉 Hair liquid

		% by weight
A	Polyoxypropylene butyl ether (40 P.O.)	15.0
	Diisopropanolamine	0.5
	6 – (4 – Hydroxy – 3 – methyl – 2 – butenylamino) – purine	8.0
	Ethanol	50.0
B	Propylene glycol	3.0
	Purified water	proper amount

Ingredients belonging to group A were uniformly stirred at ordinary temperature to make solution A. Separately, ingredients belonging to group B were uniformly dissolved and gradually added to solution A.

followed by uniform stirring to prepare a hair liquid.

〈Formulation Example 8〉 Milk lotion

		% by weight
A	Polyoxypropylene behenyl ether (20 P.O.)	0.5
	Tetraoleic acid polyoxyethylenesorbit (60 E.O.)	1.0
	Oleophilic monostearyl glyceride	1.0
	Stearic acid	1.5
	Behenyl ether	1.5
	Avocado oil	3.0
	Natural vitamin E	0.02
	6 – Phenylureidopurine	0.05
	Diphenylurea	0.05
	6 – Benzylaminopurine	1.0
B	1,3 – Butylene glycol	5.0
	Purified water	proper amount

Ingredients belonging to group A were heated to prepare solution A. Separately, ingredients belonging to group B were heated to prepare solution B. Solution B was added to solution A and emulsified, followed by cooling the emulsion to prepare a milk lotion.

〈Test Example 1〉 Hair – growing test using mouse

(1) Effect of independent application

ddY strain white mice (male, 7 – week old, 32 g in weight) in a period of telogen with total back hair were clipped from tail to back using a pair of electric fur clippers, and a sample milk lotion prepared by incorporating 1 % by weight of the effective ingredient of the present invention in a base of the formulation example 8 was applied to the clipped portion of each mouse on and after the next day of clipping, twice a day and 5 days a week in an amount of 0.2 ml per application to a mouse. Ten mouse were used for one sample.

Hair – growing effect was evaluated by comparing number of mice growing hair and hair – growing area with those of a control group on the 35th day from the start of the test. The hair – growing area was determined by photographing the tested portion, cutting out the hair – growing area of the photograph, and calculating the weight ratio of the cut – out photograph with that before the application, with ten ratios thus calculated as to mice belonging to the same group being averaged.

Additionally, mice of a control group were applied with the base alone, and mice of a positive control group were applied with a 4 % pentadecanoic acid glyceride.

Results of the test are tabulated in Table 1.

(2) Effect of combined application

Effect of combined application of the ingredients of the present invention and combined application of the ingredient of the present invention and other known effective ingredient were evaluated according to the above – described independent application. Results thus obtained are shown in Tables 2 to 11.

Additionally, the results with the control of applying only the base were: Number of hair – growing mice: 2/10; Ratio of hair – growing area: 23.1 %.

Table 1

Results of hair - growing test		
Sample	Number of Hair - growing Mice	Ratio of Hair - growing Area(%)
Control	2/10	26.3
Pentadecanoic acid glyceride	6/10	61.5
6 - Phenylaminopurine	7/10	70.5
6 - (3 - Methyl - 2 - butenylamino)purine	8/10	71.9
6 - (4 - Hydroxy - 3 - methyl - 2 - butenylamino) - purine	6/10	65.0
6 - (4 - Acetoxy - 3 - methyl - 2 - butenylamino) - purine	6/10	64.3
6 - Benzylaminopurine	9/10	79.1
6 - Phenylureidopurine	6/10	67.8
6 - (2 - Chloro - 5 - methyl - 1 - pentanylamino) - purine	8/10	74.2
6 - (2 - Phenethyl)purine	7/10	69.4
6 - Styrylpurine	8/10	80.7
6 - Isoamylaminopurine	7/10	66.1
6 - Benzylamino - 9 - ribofuranosylpurine	7/10	67.7
N - (2 - Chloro - 4 - pyridyl) - N' - phenylurea	7/10	66.6
N - (4 - Pyridyl) - N' - phenylurea	7/10	66.3
N - (2 - Trifluoromethyl - 4 - pyridyl) - N' - phenylurea	8/10	76.5
N - (2,6 - Dichloro - 4 - pyridyl) - N' - phenylurea	6/10	64.8
4 - Benzylamino - 6 - methylaminopyrimidine	7/10	70.4
4 - Phenylureidopyrimidine	6/10	65.9
N - (3 - Nitrophenyl) - N' - phenylurea	6/10	63.2
4 - Imidazolecarbanilide	6/10	64.7
Isonitotinic acid anilide	8/10	78.1
4 - (3 - methyl - 2 - butenylamino) - pyrrolo - [2,3 - d] - pyrimidine	6/10	62.2

Table 2

Results of hair-growting test

Ingredient (present invention)	Incorporated Amount (% by weight) Test Sample											
	1	2	3	4	5	6	7	8	9	10	11	12
6-Benzylaminopurine	0.3											
6-(4-Methylbenzylamino)-purine		0.3										
6-Phenylaminopurine			0.3									
6-Styrylaminopurine				0.3								
6-Benzylamino-9-ribo-furanosylpurine					0.3							
6-Phenylureidopurine						0.3						
6-(2-Phenethyl)purine							0.3					
6-(3-Methyl-2-butenyl-amino)-9-glycosylpurine								0.3				
6-(4-Methoxybenzyl-amino)purine									0.3			
N-(2-Chloro-4-pyridyl)-N'-phenylurea										0.3		
N-(2-Trifluoromethyl-4-pyridyl)-N'-phenylurea											0.3	
N-(2,6-Dichloro-4-pyridyl)-N'-phenylurea												0.3
Number of hair-growing mice	3/10	3/10	3/10	3/10	3/10	3/10	3/10	3/10	3/10	3/10	3/10	3/10
Hair-growing area (%)	38.4	39.8	37.6	38.1	35.1	34.8	36.1	35.1	37.1	32.8	31.8	29.4

Table 3

Results of hair-growing test

Ingredient (present invention)	Incorporated Amount (% by weight) Test Sample								
	13	14	15	16	17	18	19	20	21
6-Benzylaminopurine	0.3	0.3							
6-(4-Methylbenzylamino)-purine	0.3								
6-Phenylaminopurine		0.3							
6-Styrylaminopurine			0.3						
6-Benzylamino-9-ribo-furanosylpurine			0.3	0.3					
6-Phenylureidopurine				0.3	0.3				
6-(2-Phenethyl)purine						0.3	0.3		
6-(3-Methyl-2-butenyl-amino)-9-glycosylpurine								0.3	
6-(4-Methoxybenzyl-amino)purine					0.3				0.3
N-(2-Chloro-4-pyridyl)-N'-phenylurea						0.3	0.3		
N-(2-Trifluoromethyl-4-pyridyl)-N'-phenylurea								0.3	
N-(2,6-Dichloro-4-pyridyl)-N'-phenylurea									0.3
Number of hair-growing mice	8/10	8/10	7/10	6/10	7/10	7/10	6/10	7/10	7/10
Hair-growing area (%)	83.1	78.1	75.3	69.8	72.7	73.1	69.4	70.3	75.4

Table 4

Results of hair-growing test

Ingredient (present invention)	Incorporated Amount (% by weight) Test Sample											
	1	22	3	4	5	8	10	23	24	25	26	27
6-Benzylaminopurine	0.3											
6-(4-Methoxybenzyl-aminopurine		0.3										
6-Phenylaminopurine			0.3									
6-Styrylaminopurine				0.3								
6-Benzylamino-9-ribo-furanosylpurine					0.3							
6-(3-Methyl-2-butenyl-amino)-9-glucosylpurine						0.3						
N-(2-Chloro-4-pyridyl)-N'-phenylurea							0.3					
Diphenylurea								0.3				
Phenylureido-4-pyrimi-dine									0.3			
4-Imidazolecarbanide										0.3		
Isonicotinic acid anilide											0.3	
4-(3-Methyl-2-butenyl-amino)pyrrolo[2,3-d]-pyrimidine												0.3
Number of hair-growing mice	3/10	3/10	3/10	3/10	3/10	3/10	3/10	3/10	3/10	3/10	3/10	3/10
Hair-growing area (%)	38.4	39.8	37.6	38.1	35.1	31.4	32.8	32.9	30.1	32.4	29.8	28.7

Table 5

Results of hair-growing test

Ingredient (present invention)	Incorporated Amount (% by weight)								
	Test Sample								
	28	29	30	31	32	33	34	35	36
6-Benzylaminopurine	0.3	0.3							
6-(4-Methoxybenzyl-aminopurine			0.3	0.3					
6-Phenylaminopurine					0.3				
6-Styrylaminopurine						0.3			
6-Benzylamino-9-ribo-furanosylpurine							0.3		
6-(3-Methyl-2-butenyl-amino)-9-glucosylpurine								0.3	
N-(2-Chloro-4-pyridyl)-N'-phenylurea	0.3								0.3
Diphenylurea		0.3			0.3				
Phenylureido-4-pyrimi-dine			0.3			0.3			
4-Imidazolecarbanide				0.3			0.3		
Isonicotinic acid anilide								0.3	
4-(3-Methyl-2-butenyl-amino)pyrrolo[2,3-d]-pyrimidine									0.3
Number of hair-growing mice	7/10	7/10	6/10	6/10	7/10	6/10	7/10	6/10	6/10
Hair-growing area (%)	76.5	78.1	68.9	67.4	71.4	70.3	77.3	70.4	67.8

Table 6

Results of hair-growing test

Ingredient	Incorporated Amount (% by weight)								
	Test Sample								
	1	2	3	4	5	6	7	8	9
6-Benzylaminopurine*	0.3								
6-(4-Methylbenzyl-amino)purine*		0.3							
Dibutyl c-AMP**			0.5						
Forskolin**				0.5					
Carpronium chloride**					0.5				
Pentadecanoic acid glyceride**						2.0			
Capticum tincture**							0.1		
Japanese chirata extract**								0.1	
Ginseng extract**									0.1
Number of hair-growing mice	3/10	3/10	2/10	2/10	2/10	2/10	2/10	2/10	2/10
Hair-growing area (%)	38.4	39.8	32.1	30.1	30.8	28.6	22.7	25.8	27.4

*: Ingredient of the present invention

**: Ingredient used in combination with the ingredient of the present invention

Table 7 (A)

Results of hair – growing test						
Ingredient	Incorporated Amount (% by weight)					
	Test sample					
	10	11	12	13	14	15
6 – Benzylaminopurine*	0.3	0.3	0.3	0.3	0.3	0.3
6 – (4 – Methylbenzylamino)purine*						
Dibutyl c – AMP**	0.5					
Forskolin**		0.5				
Carpronium chloride**			0.5			
Pentadecanoic acid				2.0		
glyceride**						
Capticum tincture**					0.1	
Japanese chirata extract**						0.1
Ginseng extract**						
Number of hair – growing mice	9/ 10	9/ 10	9/ 10	9/ 10	8/ 10	8/ 10
Hair – growing area (%)	89.1	90.3	91.5	88.7	86.5	84.3

*: Ingredient of the present invention

**: Ingredient used in combination with the ingredient of the present invention

Table 7 (B)

Results of hair - growing test						
Ingredient	Incorporated Amount (% by weight)					
	Test sample					
	16	17	18	19	20	21
6 - Benzylaminopurine*						
6 - (4 - Methylbenzylamino)purine*	0.3	0.3	0.3	0.3	0.3	0.3
Dibutyl c - AMP**	0.5					
Forskolin**		0.5				
Carpronium chloride**						
Pentadecanoic acid glyceride**			2.0			
Capticum tincture**				0.1		
Japanese chirata extract**					0.1	
Ginseng extract**						0.1
Number of hair - growing mice	9/ 10	9/ 10	9/ 10	8/ 10	8/ 10	8/ 10
Hair - growing area (%)	90.3	89.1	90.4	87.2	84.6	85.7

*: Ingredient of the present invention

**: Ingredient used in combination with the ingredient of the present invention

Table 8

Results of hair – growing test										
Ingredient	Incorporated Amount (% by weight)									
Ingredient	Test Sample									
	22	23	24	25	6	5	8	26	7	27
6 – Phenylaminopurine*	0.3									
6 – Styrylpurine*		0.3								
6 – Benzylamino – 9 – ribofuranosylpurine*			0.3							
Minoxidil**				0.5						
Pentadecanoic acid glyceride**					0.5					
Carpronium chloride**						0.5				
Japanese chirata extract**							0.1			
Estradiol**								0.5		
Capticum tincture**									0.1	
Ginger extract**										0.1
Number of hair – growing mice	3/ 10	3/ 10	3/ 10	2/ 10	2/ 10	2/ 10	2/ 10	2/ 10	2/ 10	2/ 10
Hair – growing area (%)	37.6	38.1	35.1	28.1	28.6	30.8	25.8	25.9	22.7	26.1

*: Ingredient of the present invention

**: Ingredient used in combination with the ingredient of the present invention

Table 9

Results of hair – growing test											
Ingredient	Incorporated Amount (% by weight)										
	Test Sample										
	28	29	30	31	32	33	34	35	36	37	38
6 – Phenylaminopurine*	0.3	0.3	0.3	0.3							
6 – Styrylpurine*					0.3	0.3	0.3				
6 – Benzylamino – 9 – ribofuranosylpurine*								0.3	0.3	0.3	0.3
Minoxidil**	0.5				0.5						
Pentadecanoic acid glyceride**		2.0				2.0		2.0			
Carpronium chloride**									0.5		
Japanese chirata extract**			0.1								
Estradiol**				0.5						0.5	
Capticum tincture**							0.1				
Ginger extract**											0.1
Number of hair – growing mice	9/ 10	8/ 10	8/ 10	8/ 10	9/ 10	9/ 10	8/ 10	9/ 10	9/ 10	8/ 10	8/ 10
Hair – growing area (%)	89.5	82.1	83.6	84.9	90.3	91.5	84.5	89.7	90.5	86.5	87.8

*: Ingredient of the present invention

**: Ingredient used in combination with the ingredient of the present invention

Table 10 (A)

Results of hair – growing test						
Ingredient	Incorporated Amount (% by weight)					
	Test Sample					
	39	40	41	42	43	44
N – (2 – Chloro – 4 – pyridyl) – N' – phenylurea*	0.3					
Diphenylurea*		0.3				
Phenylureido – 4 – pyrimidine*			0.3			
4 – Imidaaolecarbanilide*				0.3		
Isonicotinic acid anilide*					0.3	
4 – (3 – Methyl – 2 – butenylamino)pyrrolo[2,3 – d]pyrimidine*						0.3
Number of hair – growing mice	3/ 10	3/ 10	3/ 10	3/ 10	3/ 10	3/ 10
Hair – growing area (%)	32.8	33.9	31.9	34.3	32.8	33.9

*: Ingredient of the present invention

Table 10 (B)

Results of hair – growing test						
Ingredient	Incorporated Amount (% by weight)					
	Test Sample					
	25	5	6	26	7	8
Minoxidil**	0.5					
Carpronium chloride**		0.5				
Pentadecanoic acid glyceride**			2.0			
Estradiol**				0.5		
Capticum tincture**					0.1	
Japanese chirata extract**						0.1
Number of hair – growing mice	2/ 10	2/ 10	2/ 10	2/ 10	2/ 10	2/ 10
Hair – growing area (%)	28.1	30.8	28.6	25.9	22.7	25.8

**: Ingredient used in combination with the ingredient of the present invention

Table 11

Results of hair – growing test									
Ingredient	Incorporated Amount (% by weight)								
	Test Sample								
	45	46	47	48	49	50	51	52	53
N – (2 – Chloro – 4 – pyridyl) – N' – phenylurea*	0.3	0.3							
Diphenylurea*			0.3	0.3					
Phenylureido – 4 – pyrimidine*					0.3	0.3			
4 – Imidaaolecarbanilide*							0.3		
Isonicotinic acid anilide*								0.3	
4 – (3 – Methyl – 2 – butenylamino)pyrrolo[2,3 – – d]pyrimidine*									0.3
Minoxidil**	0.5		0.5						
Carpronium chloride**		0.5			0.5				
Pentadecanoic acid glyceride**				2.0		2.0			
Estradiol**							0.5		
Capticum tincture**								0.1	
Japanese chirata extract**									0.1
Number of hair – growing mice	7/ 10	6/ 10	7/ 10	6/ 10	6/ 10	6/ 10	7/ 10	7/ 10	6/ 10
Hair – growing area (%)	76.8	69.3	75.9	69.8	67.3	70.4	71.8	73.9	69.6

*: Ingredient of the present invention

**: Ingredient used in combination with the ingredient of the present invention

As is demonstrated above, the ingredients of the present invention show a remarkable effect of promoting hair growth.

〈Test Example 2〉 Clinical test

Results of clinical test on the curing effect of the ingredients of the present invention for male alopecia.

1) Preparation of samples

Test samples were prepared by respectively incorporating 13 effective ingredients of the present invention of 6 – styrylpurine, 6 – benzylaminopurine, 6 – benzylamino – 9 – ribofuranosylpurine, N – (2 – chloro – 4 – pyridyl) – N' – phenylurea, N – (2 – trifluoromethyl – 4 – pyridyl) – N' – phenylurea, N – (2,6 – dichloro – 4 – pyridyl) – N' – phenylures, 6 – (4 – methylbenzylamino)purine, 6 – (4 – methoxybenzylamino) – purine, 6 – (4 – methylsulfonylbenzylamino)purine, 6 – phenylureidopurine, 6 – (2 – phenethyl)purine, diphenylurea and phenylureido – 4 – pyrimidine in the preparation of formulation example 2 (base) in an amount of 0.5 %. Control samples were prepared by using only a base or by respectively incorporating pentadecanoic acid glyceride and carpronium chloride in an amount of 1 %.

2) Subjects

480 male volunteers suffering from alopecia were selected and grouped at random into 16 groups each of which were composed of 30 subjects.

3) Testing method

A suitable amount of each sample preparation was applied to the head ranging from the front portion of the head to the top portion thereof twice a day (morning and night) for 4 months.

4) Evaluation of curing effect

Upon completion of the application over four months, hair condition (degree of epilation, sprouting of fine soft hair, change in hair quality) was examined in comparison with that before application by reference to photographic pictures in 5 grades (A: remarkably improved; B: middlingly improved; C: slightly improved; D: no changes; E: changes for the worse). As to side effects, scalp was checked for ruber, pimple and like abnormality after the 4 – month application.

5) Standard of evaluation

(1) Degree of epilation
- A: Epilation was scarcely observed, thus alopecia being overcome.
- B: Epilation was considerably reduced.
- C: Epilation was slightly reduced.
- D: Epilation was not reduced at all.
- E: Epilcation was increased.

(2) Growing of fine soft hair
- A: Extremely many fine soft hairs were observed to grow.
- B: Considerably many fine soft hairs were observed to grow.
- C: Fine soft hairs were observed to slightly sprout.
- D: Growing of fine soft hair was not observed at all.
- E: Fine soft hairs were observed to decrease in number.

(3) Change in hair quaity
- A: Soft hairs were scaresely observed, thus hair condition being normalized as to hair quaity.
- B: Soft hairs were made considerably harder.
- C: Soft hairs were made slightly harder.
- D: No changes were found as to hair quality.
- E: Soft hairs increased in number.

(5) Results

Results tabulated in the following Tables 12 to 14 were obtained.

Table 12

Degree of epilation

Incorporated Effective Ingredient	A	B	C	D	E	Side Effect	Total	Improved Ratio (%)
6-Styrylpurine*	11	9	7	3	0	0	30	67
6-Benzylaminopurine*	14	9	5	2	0	0	30	77
6-Benzylamino-9-ribofuranosylpurine*	11	12	4	3	0	0	30	77
N-(2-Chloro-4-pyridyl)-N'-phenylurea*	10	13	6	1	0	0	30	77
N-(2-Trifluoromethyl-4-pyridyl)-N'-phenylurea*	12	4	10	4	0	0	30	53
N-(2,6-Dichloro-4-pyridyl)-N'-phenylurea*	14	8	5	3	0	0	30	73
6-(4-Methylbenzylamino)purine*	11	10	4	5	0	0	30	70
6-(4-Methoxybenzylamino)purine*	12	10	5	3	0	0	30	73
6-(4-Methylsulfonylbenzylamino)purine*	11	11	3	5	0	0	30	73
6-Phenylureidopurine*	10	9	4	7	0	0	30	63
6-(2-Phenethyl)purine*	10	8	5	7	0	0	30	60
Diphenylurea*	4	12	8	6	0	0	30	53
Phenylureido-4-pyrimidine*	5	11	6	8	0	0	30	53
Base ingredients alone**	0	0	3	25	0	0	30	0
Pentadecanoic acid Glyceride**	2	12	7	9	0	0	30	47
Carpronium chloride**	0	2	16	12	0	1	30	7

": Group of tested ingredients of the present invention

"": Group of control

Note: Numerals in the above table designate numbers of subjects. Improved ratio is a ratio of number of subjects scored A and B to the total number of 30.

Table 13

Growing of soft hair

Incorporated Effective Ingredient	A	B	C	D	E	Side Effect	Total	Improved Ratio (%)
6-Styrylpurine*	13	7	8	2	0	0	30	67
6-Benzylaminopurine*	15	10	4	1	0	0	30	83
6-Benzylamino-9-ribofuranosylpurine*	12	13	3	3	0	0	30	83
N-(2-Chloro-4-pyridyl)-N'-phenylurea*	11	8	10	1	0	0	30	63
N-(2-Trifluoromethyl-4-pyridyl)-N'-phenylurea*	8	16	6	0	0	0	30	80
N-(2,6-Dichloro-4-pyridyl)-N'-phenylurea*	8	14	7	1	0	0	30	73
6-(4-Methylbenzylamino)purine*	11	10	7	2	0	0	30	70
6-(4-Methoxybenzylamino)purine*	10	10	7	3	0	0	30	67
6-(4-Methylsulfonylbenzylamino)purine*	10	12	7	1	0	0	30	73
6-Phenylureidopurine*	9	10	4	7	0	0	30	63
6-(2-Phenethyl)purine*	10	9	5	6	0	0	30	63
Diphenylurea*	5	12	4	9	0	0	30	57
Phenylureido-4-pyrimidine*	5	13	4	8	0	0	30	60
Base ingredients alone**	0	0	2	28	0	0	30	0
Pentadecanoic acid Glyceride**	3	13	2	12	0	0	30	53
Carpronium chloride**	1	4	10	15	0	1	30	17

*: Group of tested ingredients of the present invention

**: Group of control

Note: Numerals in the above table designate numbers of subjects. Improved ratio is a ratio of number of subjects scored A and B to the total number of 30.

Table 14

Change in hair quality

Incorporated Effective Ingredient	A	B	C	D	E	Side Effect	Total	Improved Ratio (%)
6-Styrylpurine"	11	12	8	1	0	0	30	77
6-Benzylaminopurine"	14	6	7	3	0	0	30	67
6-Benzylamino-9-ribofuranosylpurine"	13	5	9	3	0	0	30	60
N-(2-Chloro-4-pyridyl)-N'-phenylurea"	9	6	13	2	0	0	30	50
N-(2-Trifluoromethyl-4-pyridyl)-N'-phenylurea"	10	7	12	1	0	0	30	57
N-(2,6-Dichloro-4-pyridyl)-N'-phenylurea"	14	6	5	5	0	0	30	67
6-(4-Methylbenzylamino)purine"	11	7	8	4	0	0	30	60
6-(4-Methoxybenzylamino)purine"	10	9	8	3	0	0	30	63
6-(4-Methylsulfonylbenzylamino)purine"	9	9	7	5	0	0	30	60
6-Phenylureidopurine"	8	10	8	4	0	0	30	60
6-(2-Phenethyl)purine"	7	11	6	6	0	0	30	60
Diphenylurea"	6	11	6	7	0	0	30	57
Phenylureido-4-pyrimidine"	5	12	7	6	0	0	30	57
Base ingredients alone""	0	0	4	23	3	0	30	0
Pentadecanoic acid Glyceride""	3	12	7	8	0	0	30	50
Carpronium chloride""	0	4	15	10	1	1	30	17

": Group of tested ingredients of the present invention

"": Group of control

Note: Numerals in the above table designate numbers of subjects. Improved ratio is a ratio of number of subjects scored A and B to the total number of 30.

As is shown above, the ingredients of the present invention exhibited better effect of curing alopecia than the control ingredients.

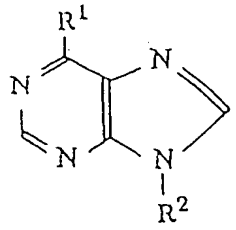
The preparation of the present invention for promoting hair growth exhibits an excellent effect of promoting hair growth or curing alopecia such as male alopecia or alopecia areata and can be applied to scalp for prophylaxis of alopecia and curing various alopecia diseases with no serious side effects.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description, and all the changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

Claims

1. A hair growth-promoting preparation which contains, as an effective ingredient, one or more compounds selected from the group consisting of purine compounds, pyridylurea compounds, diphenylurea compounds, pyrimidine compounds, imidazole compounds, benzoylaminourea compounds and 4-substituted aminopyrrolo[2,3-d]pyrimidine compounds.

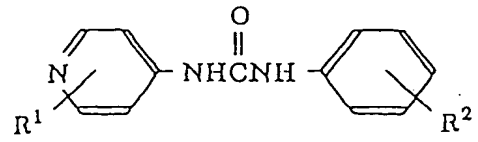
2. The hair growth-promoting preparation as described in claim 1, wherein said purine compounds are those which are represented by the following general formula (1):



(1)

wherein R^1 represents an alkyl group having 1 to 22 carbon atoms, a cyclic hydrocarbon group, an alkenyl group having 1 to 22 carbon atoms, a substituted or non-substituted aralkyl group, a substituted or non-substituted styryl group, an alkylamino group, an amino group having a cyclic hydrocarbon group, an alkenylamino group, a substituted or non-substituted benzylamino group, a substituted or non-substituted phenylethylamino group, a substituted or non-substituted phenylamino group, a substituted or non-substituted phenylaminocarbonylamino group, a pyridylamino group, a pyridylmethylamino group, a pyrrolylmethylamino group, an oxazolylmethylamino group, an imidazolylmethylamino group, a pyridazinylmethylamino group, a naphthylamino group or a naphthylmethylamino group, and R^2 represents a hydrogen atom or a pentose or hexose residue.

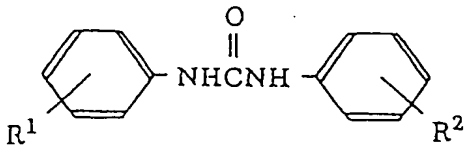
3. The hair growth-promoting preparation as described in claim 1, wherein said pyridylurea compounds are those which are represented by the following general formula (2):



(2)

wherein R^1 and R^2 may be the same or different and each represents a hydrogen atom or represents one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, a chlorine atom, a hydroxy group, a fluorine atom, a nitro group, a bromine atom, a cyano group, an acetamino group, a methoxycarbonyl group, a dimethylamino group, a methoxy group, a trimethylsilyl group, a trifluoromethyl group, a butyldimethylsilyloxy group, a methylthio group, a trimethylsilyloxy group, an acetoxy group, a propionyloxy group, a methylsulfinyl group, a methylsulfonyl group, a carboxyl group, a methoxycarbonyl group and an ethoxycarbonyl group.

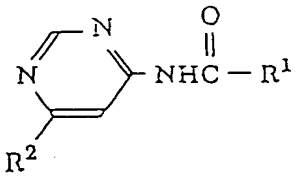
4. The hair growth-promoting preparation as described in claim 1, wherein said diphenylurea compounds are those which are represented by the following general formula (3):



(3)

wherein R^1 and R^2 may be the same or different and each represents a hydrogen atom or represents one or more substituents selected from the group consisting of an alkyl group having 1 to 6 carbon atoms, a chlorine atom, a hydroxy group, a fluorine atom, a nitro group, a bromine atom, a cyano group, an acetamino group, a methoxycarbonyl group, a dimethylamino group, a methoxy group, a trimethylsilyl group, a trifluoromethyl group, a butyldimethylsilyloxy group, a methylthio group, a trimethylsilyloxy group, an acetoxy group, a propionyloxy group, a methylsulfinyl group, a methylsulfonyl group, a carboxyl group, a methoxycarbonyl group and an ethoxycarbonyl group.

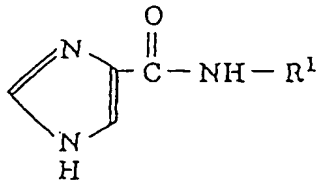
5. The hair growth-promoting preparation as described in claim 1, wherein said pyrimidine compounds are those which are represented by the following general formula (4):



(4)

wherein R^1 represents a substituted or non-substituted phenyl group or a substituted or non-substituted anilino group, and R^2 represents a hydrogen atom, a methyl group, an ethyl group, a butyl group, a propyl group, a chlorine atom, a hydroxy group, a fluorine atom, a nitro group, a bromine atom, a cyano group, an acetamino group, a methoxycarbonyl group, a dimethylamino group, a methoxy group, a trimethyloxy group, a trifluoromethyl group, a butyldimethylsilyloxy group, a methylthio group, a trimethylsilyloxy group, an acetoxy group, a propionyloxy group, a methylsulfinyl group, a methylsulfonyl group, a carboxyl group, a methoxycarbonyl group or an ethoxycarbonyl group.

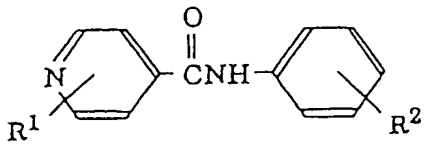
6. The hair growth-promoting preparation as described in claim 1, wherein said imidazole compounds are those which are represented by the following general formula (5):



(5)

wherein R^1 represents a substituted or non-substituted phenyl group.

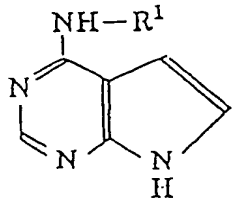
7. The hair growth-promoting preparation as described in claim 1, wherein said bensoylaminourea compounds are those which are represented by the following general formula (6):



(6)

wherein R^1 represents a hydrogen atom, an alkyl group, a halogen atom, a hydroxy group, a cyano group, an acetamino group, an alkyloxycarbonyl group, an alkylamino group, a methoxy group, an alkylsilyloxy group, an alkylthio group, an acetoxy group, an alkylcarbonyloxy group, an alkylsulfinyl group, an alkylsulfonyl group or a carboxyl group, and R^2 represents a hydrogen atom, or one or more substituents selected from the group consisting of a methyl group, an ethyl group, a butyl group, a propyl group, a chlorine atom, a hydroxy group, a fluorine atom, a nitro group, a bromine atom, a cyano group, an acetamino group, a methoxycarbonyl group, a dimethylamino group, a methoxy group, a trifluoromethyl group, a butyldimethylsilyloxy group, a methylthio group, a trimethylsilyloxy group, an acetoxy group, a propionyloxy group, a methylsulfinyl group, a methylsulfonyl group, a carboxyl group, a methoxycarbonyl group and an ethoxycarbonyl group.

8. The hair growth-promoting preparation as described in claim 1, wherein said 4-substituted aminopyrrolo[2,3-d]pyrimidine compounds are those which are represented by the following general formula (7):



(7)

wherein R^2 represents a substituted or non-substituted benzyl group, a substituted or non-substituted phenylaminocarbonyl group or a furfuryl group.

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(54) **Preparation for promoting hair growth.**

(57) A preparation for promoting hair growth is disclosed, which contains as an effective ingredient or ingredients one or more compounds selected from the group consisting of purine compounds, pyridylurea compounds, diphenylurea compounds, pyrimidine compounds, imidazole compounds, benzoylaminourea compounds and 4-substituted aminopyrrolo[2,3-d]pyrimidine compounds. This preparation exhibits an excellent effect of promoting hair growth or curing alopecia such as male alopecia or alopecia areata. Of the effective compounds, purine compounds and pyridyl compounds exhibit particularly remarkable effects.

EP 0 540 854 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 11 5434

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	PATENT ABSTRACTS OF JAPAN vol. 12, no. 316 (C-524)(3163) & JP-A-63 88 112 (DAI ICHI SEIYAKU CO.) * abstract *	1	A 61 K 7/06
X	FR-A-1 440 795 (LABORATOIRES DU DOCTEUR JACQUES AUCLAIR) * the whole document *	1	
X	DE-A-3 210 669 (KRNJEVIC) * example 4 *	1	
X	EP-A-0 387 757 (BIORESEARCH S.P.A.) * the whole document *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	18-01-1993	FISCHER J P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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European Patent Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,
namely:

See sheet -B-

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid,

namely claims:

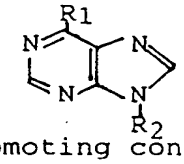
☒ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

namely claims: 1 (partially) and 2

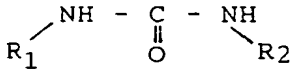
LACK OF UNITY OF INVENTION A PRIORI

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

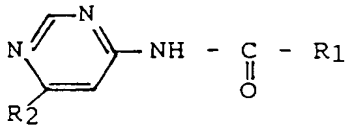
1. Claims: 1-2 (1 partially) Hair growth-promoting containing purine compounds:



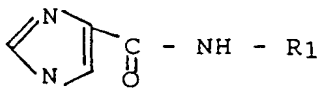
2. Claims: 3-4 Hair growth-promoting containing urea derivatives:



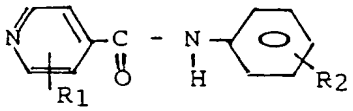
3. Claim: 5 Hair growth-promoting containing pyrimidine compounds:



4. Claim: 6 Hair growth-promoting containing imidazole compounds:



5. Claim: 7 Hair growth-promoting containing an amide of the type:



6. Claim: 8 Hair growth-promoting containing an amino-pyrrolo (2,3-d)pyrimidine compound: